## Remarks

### The Amendment

Claim 13 as amended remains the sole independent claim pending. Claim 13 has been amended to describe the end of the target polynucleotide to be sequenced as the "first" end and to describe the other end as the "second" end in the claim. These amendments do not introduce new matter.

### The Rejection under Section 102(b) Should Be Withdrawn

The examiner maintained the rejection of claim 8-9 and 11-16 as purportedly being anticipated by Jones *et al.* WO00/39333, asserting that the published application teaches a method for determining the sequence of a polynucleotide comprising i) treating a sample of a double stranded target polynucleotide to create overhangs at each end having defined number of bases in each overhang (page 33, line 17-35, page 54, line 13-22); ii) dividing sample and contacting each sample with a signal sequence and a double stranded adapter sequence and ligating said sequences (page 54, line 19-31); iii) carrying out polymerase chain reaction using primers that hybridize to the ends of the polynucleotide, optionally repeating the steps (page 54, line 32-37); iv) identifying the presence of the signal sequences on the amplified products, in which order, and determining the sequence of the target polynucleotide (page 55, lines 1-6, page 36- lines 24-37). The examiner indicated that claim 13 does not distinguish the first and second ends of the target sequence or specify that the signal sequence recited is added to the second end.

In response, while Applicants believe the claim was clear as previously presented, Applicants have amended independent claim 13 to more clearly specify a first end (to be sequenced) and a second end (the end opposite the end to be sequenced) of the target sequence and that the recited signal sequence is hybridized and ligated to the second end. In contrast to the Jones *et al.* published application, the method according to claim 13 requires that the signal sequence represents theoverhang to be sequenced but it is ligated to the end of the target polynucleotide opposite to the end it represents. The adaptor is ligated to the end of the target polynucleotide that is to be sequenced and is cleaved off after each round of sequencing. Therefore, the target polynucleotide increase in length at the end opposite to the end being sequenced as successive signal sequences are ligated to that opposite end. The end of the target that is sequenced is reduced in length following each successive round of

sequencing, as each overhang is cleaved to reveal a new overhang once a signal sequence representing the overhang has been ligated to the other end of the target polynucleotide. This feature of the method appears in step (ii) of claim 13 and differs from the method disclosed in the Jones *et al.* published application wherein the signal sequences (magnifying tags) are ligated to the end of the target that is being sequenced (i.*e.*, are ligated to the end they represent).

Claim 13 and its dependent claims as presented herein are therefore directed to novel subject matter and the rejection under Section 102(b) should be withdrawn.

The Rejection under Section 103(a) Should Be Withdrawn

The examiner rejected claim 10 as purportedly obvious over Jones *et al.* WO00/39333 in view of Sorge *et al.* U.S. Patent No. 6,017,701. The examiner argued that it would have been obvious to use 5-methyl-dCTP nucleotides of the U.S. patent (col. 8, lines 46-64, col. 19, lines 27-52) in the method of the published application (described above) and that it would have been obvious that the combination would result in a sensitive and enhanced method for detecting specific target nucleic acid sequences. Again, the examiner indicated that claim 13 does not distinguish the first and second ends of the target sequence or specify that the signal sequence recited is added to the second end.

In response, Applicant submits that the Jones *et al.* published application does not suggest the method of claim 10 as dependent on claim 13 nor does the Sorge *et al.* patent remedy the deficiencies of the published application.

More specifically, in the Jones *et al.* published application, the moiety comprising the magnified tag (which corresponds to the signal sequence of the present invention) is ligated to the portion of the target polynucleotide that it represents. As sequencing progresses, the signal sequences are added to the sequenced end of the target polynucleotide.

In contrast, in methods of the present invention, the signal sequence hybridizes to the end of the target molecule opposite the end at which the portion of the target sequence that it represents is located. The adapter is ligated to the end of the target polynucleotide to be sequenced and is cleaved after each round of amplification. The adapter, which is complementary to the sequence represented by the signal sequence, will hybridize to the portion of the target that is to be represented by the signal sequence only if the sequence of the adapter is also complementary to this portion of the target sequence. In contrast, the

signal sequence will ligate to the opposite end of each of the samples, regardless of its complementarity to the target sequence. However, polymerase amplification can only proceed exponentially if both the adapter and signal sequences are ligated to the target polynucleotide, since both are required for primer recognition. Therefore, the only samples which will be amplified are those wherein the adapter, being complementary to the sequence represented by the signal sequence, is also complementary to the target overhang, thereby identifying the sample in which the sequence represented by the signal sequence is identical to the portion of the target sequence to be identified.

Thus, the Jones *et al.* published application does not suggest the method of amended claim 10 herein and its combination with the Sorge *et al.* patent correspondingly fails to suggest the method of the dependent claims. The rejection under Section 103(a) should therefore be withdrawn.

## Conclusion

The claims as listed are believed to be in condition for allowance and early notice of the same is respectfully requested.

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